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EXAMINER
BERCH, MARK L

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1624	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/982,351	Applicant(s) GANGJEE, ALEEM
	Examiner Mark L. Berch	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 29-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 29-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 22 is rejected under 35 U.S.C. 102(e) as being anticipated by 6562969.

In 6562969, see Table 5, compounds 6 and 9. These correspond to X = heteroalkyl, wherein the alkyl is methyl, and the heteroatom which replaces the methyl is oxygen. Alternatively, X is heteroalkylene, and R1 is H. X2R3 is methyl or phenylethyl, with R3 = phenyl in the latter.

Claims 22, 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Jun, Bulletin of the Korean Chemical Society 17(8), 676-678 (1996).

Note in Scheme 3, the species 4d which corresponds to X = NH, R1 = H, X2 = methyl.

Claims 22, 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Taylor.

Note the species 6 which appears to correspond to R3 as aroylglutamate, although this is not certain (see issue 3 in the rejection below). The compound is an antitumor agent.

Claims 22, 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Benghiat.

Note the species 9. This corresponds to X2 as heteroalkylene, with one replacement of C with S, and R3 as heterocyclic, specifically, the adenosine part.

Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Secrist et al.

See Table 1, compounds 5a and 5b. 5a is the species of 6562969. 5b corresponds to X2 as heteroalkenylene with 2 carbons replaced by oxygens, and R3 as methyl at the end.

Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Farkas.

Note the Table II, 6th species, which corresponds to X2 as heteroalkyl, with one C replaced by a N.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 34 rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor or Benghiat.

The utility is as given in these reference. It would be obvious to administer such a drug via one of these three means, since collectively, thee cover nearly all modes of drug administration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 29-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The meanings quoted by applicants are not the usual meaning at all. Alkyl is a group of the formula $-C_nH_{2n+1}$, as is set forth in such sources as Hack's Chemical Dictionary and Hawley's Condensed Chemical Dictionary, or any textbook of organic chemistry. As such it cannot have rings. Thus, reliance on this material, and the use of "cyclic lower alkyl" at e.g. third from last line of claim 22 renders the claims indefinite.
2. For X and X2, the "about 3 atoms" is indefinite. Does this cover 4? 5? 6? 7?

3. The term "p-aroyl-glutamate" is unclear. Where is it bound? Via the O? N? via a Carbon? And where exactly in the aroyl?
4. The scope of claim 29 is unclear, insofar as the two processes are concerned. The claim has both "inhibiting" and "for treatment of a disease condition". It is unclear whether the claim requires just "inhibiting" just "for treatment of a disease condition", or both. The enablement rejection below assumes that any of these interpretations might be the correct one.
5. Claim 31's wording does not make sense. Cell proliferation and angiogenesis are not disease conditions. These are normal, and indeed, essential body processes. If either of them were to stop, the human body would die in a short period of time.
6. Further, the terms seem to heavily overlap. Cell proliferation covers both of the other two terms, so why are the other two terms needed?
7. Claims 36, 38-43, 45, 47-52 are misnamed, Thus, benzene is a molecule, not a moiety. Correct for claim 39 would be phenyl.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is no way of knowing what diseases this claim covers in the disease part. The scope is unknown. Which diseases are these? Determining whether a given disease responds or does not respond to such inhibition will surely involve undue experimentation. Suppose that a given Inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different inhibitors must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

This process then must be repeated with all 59 known RTKs, plus the other enzymes. As set forth below, very little is known about what disease are mediated by

these enzymes. Is there any disease which applicants can state definitely does not fall within the ambit of this claim language?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claims 29-31, 34 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of DHFR and TS, or for the diseases of claim 32, does not reasonably provide enablement for the rest of the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. The scope of the compounds is unclear. See 35 USC 112 paragraph 2 rejection above. Note also that the scope of the claims is much smaller than the scope of the invention. Owing to the broad range of the four variables, Formula (3) covers billions if not trillions of compounds.

(b) Scope of the enzymes and diseases covered. The claim covers inhibiting any RTK, plus two other enzymes. Note the cited reference Receptor Tyrosine Kinases (RTKs) chart from http://www.kinase.com/mammalian/rtks.pdf This shows that there is in fact a entire family with over 20 sub-families, and 59 specific enzymes. And these are just the human ones; there are mouse isologs, and ones for zebra fish, worms, etc. Moreover, these are not at all equivalent to each other.

In terms of the diseases, claim 22 covers any "disease condition in a patient, mediated by inhibition of any of these enzymes." For reasons set forth above in the above 35 USC 112 paragraph 2 rejection of claim 29, it is unknown what the scope of these diseases are. It may cover most diseases, possibly nearly all diseases.

In terms of diseases, claim 31 covers three:

a) "Tumor growth" This would appear to cover most cancers, essentially, all solid tumors. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body. Further, "tumor" covers more than just cancers. It also covers many neoplasms, cancerous or not. A neoplasm is any abnormal tissue that grows by cellular proliferation more rapidly than normal, or continues to grow after the stimulus that initiated the new growth has ceased, or shows lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or

malignant. Thus, such a term also covers precancerous conditions such as lumps, lesions, and polyps. In addition, "tumor" covers things other than neoplasms. It also covers any kind of swelling arising from inflammation. Thus, the claim would appear to cover treatment of many kinds of inflammation.

b) "Cell proliferation" This is unclear for reasons set forth above; basically, cell proliferation itself not a disease condition. It is an essential body process. It could be that applicants intend any disease which involved cells proliferation. If so, it would cover most diseases.

c) "Angiogenesis" This is unclear for reasons set forth above; basically, angiogenesis itself not a disease condition. It is an essential body process, covering any formation of new blood vessels. It is in fact, a type of cell proliferation.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is almost non-existent. No dosage information whatsoever appears.

(4) State of the Prior Art: These compounds are 2-amino pyrrolo[2,3-d]pyrimidines with a specific substitution pattern. So far as the examiner is aware no 2-amino pyrrolo[2,3-d]pyrimidines are in use in medicine.

In terms of the RTKs, the prior art knows that these are quite diverse in their impact on the body. These are not at all equivalent to each other. Thus, the Eph family

of receptor protein tyrosine kinases and their ligands, the ephrins, have a role in developmental neurobiology as molecular guides for axons and may be involved in other processes such as cancer, angiogenisis, haematopoiesis, and kidney development. INSR and IRR are insulin receptors. ROS might have a role in mael fertility. Axl and Mer are involved in Homeostatic Regulation of the Immune System. Ror2 appears to have a significant role in cartilage and growth plate development. MUSK apparently is vital in assembling acetylcholine receptors at the neuromuscular junction. Others are involved in others activities, and some (e.g. CCK4, SuRTK106 or LTK) have activities which are poorly understood, or not at all. Some are even orphan receptors, with no characterized ligand, such as RYK and ROS. The connection between these activities and disease, if any, is often very little understood.

In terms of cancer: The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect just a single organ are often not

generally treatable. As an example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. That is, there is no one compound that can treat these generally, or even most of them, nor is there any reason to think that there could be such a compound.

In this regard, it is possible that applicants are arguing that an anticancer effect can arise from the fact that the compounds are supposed to inhibit angiogenisis. The prior art teaches that the regulation of angiogenisis is extraordinarily complex in the body. Numerous anti-angiogenesis factors have been identified in the body. Some of these are proteolytic fragments, such as angiostatin, Endostatin, Canstatin, Serpin antithrombin, PEX, Prolactin, Restin, Tumstatin, Arresten, Vasostatin, Kringle1-5, and Fibronectin fragments. There are also assorted cytokines and chemokines. These include IL-1 IL-4, IL-6, IL-10, IL-12 and IL-18, interferon-α, -β, and -γ, EMAP-II, gro-β, IP-10, PF4, MIG and Platelet factor 4. There are also soluble receptors FGFR-1 and VEGFR-1 and the collagenase inhibitors TIMP-1, -2, -3, and -4. There are tumor suppressor genes p16 and p53. And there are all manner of others, including TGF-β, angiopoietin, angiotensin, SPARC, ChDI, angiotensin-2-receptor, caveolin, Retinoic acid, Troponin-1, Transforming growth factor β1, Thrombospondin-1, and -2, protamine, RGD sequence, Prostate specific antigen (PSA) Osteopontin cleavage product, 2-methoxy estradiol, pigment epithelium derived factor, and others. In opposition to these are the endogenous pro-angiogenesis factors in the body. These include numerous growth factors, such as TGF-β, VEGF-A, -B, -C, -D, -E , VEGF-R2,

placental growth factor, aFGF, hepatocyte growth factor, platelet-derived growth factors (of which there are four, PDGF-A, -B, -C, and –D, which can form homodimers and heterodimers, most importantly PDGF-BB), Platelet-derived endothelial cell growth factor (PD-ECGF), BFGF, HGF, IGF-1, EGF, Granulocyte colony-stimulating factor, and others. There are also cytokines and chemokines, including α-TNF IL-1, IL-6, IL-8, IL-13, IL-15, IL-18, transferrin, Basic Fibroblast Growth Factor (bFGF), ENA-78, Gro-α, CTAP-III, MCP-1, Fractalkine SDF-1 and others. There are cell Adhesion molecules, including Soluble E-selectrin, Soluble VCAM-1, Endoglin, CD31 (PECAM-1), CD34, MUC-18, sLx, Lewis-Y/H, MUC18, $\alpha_v\beta_3$ integrin and other β1 and β3 integrins, and others. There are also some enzymes, notably cathepsin, gelatinase A and B, and stromelysin. Others include copper ions, angiostatin-2, midkine, angiopoietin-1, nitric oxide synthase, CYR61 and CTGF, Angiotropin, prostaglandin E2, Angiogenin, Adrenomedullin, thrombopoietin, IGF-1, IGF-2, plasminogen activator inhibitor 1, thymidine phosphorylase, PAF, Prolactin, Substance P, pleiotropin, endothelin, human uterine angiogenesis factor (HUAF), erythropoeitin, urokinase tissue plasminogen activator, HBNF, Corpus luteum angiogenic factor (CLAF), B61, Type I collagen, Heparin, laminin, tenascin, Fibronectin, histamine, nicotinamide, adenosine, lactic acid, ACE, HAF and others. Even this listing, however, understates the complexity of this field. Thus, VEGF-A was listed as a growth factor. In fact, it has 6 isoforms, VEGF121, VEGF145, VEGF165, VEGF183, VEGF189 and VEGF206, produced by alternate splicing of the gene ("splice variants"). All six of these are expressed in varying degrees by solid tumors, and there is in fact evidence that these might have differing biological functions.

The extreme complexity of this entire system is seen by the fact that so far three factors, IL-1, IL-6 and TGF-β have been identified as operating both pro-angiogenesis and anti-angiogenesis, depending on circumstances.

(5) Working Examples: There are no working examples for the treatment of any diseases whatsoever. What does appear is a Table of results on page 26. The first 11 compounds correspond to the claims. The others are of unknown structure, and probably relate to compounds that do not fall within the ambit of the claims. This material is of extremely limited value for the following reasons:

a) The compounds tested are not representative of the genus as a whole, because they are all extremely similar. All of them correspond to X = NH, all have R1 as meta-bromophenyl, all have X2 as methylene, and all have R3 as an optionally substituted or fused phenyl ring.

b) The kinase inhibition testing data is not representative of RTKs as a whole either. Only 4 are tested. There are, for example, none from the largest family. In addition, one of them is ambiguous. The table just says PDGFR. But there are actually two such kinases, denoted PDGFRα and PDGFRβ; they are significantly different and have different effects in the body.

c) The kinase inhibition results are generally very unimpressive. For both PDGFR and Flt-1, more than half of the compounds showed no activity at all. This is clear evidence that these compounds do not inhibit RTKs generally. Indeed, only one compound showed any activity at all against all 4 RTKs, and only one was active against 3 of the 4. Further, many of these results show only a low level of activity. Double digit value in these IC(50) results would generally be understood as having little actual value. The last

three columns are impossible to evaluate. No description of these tests is actually given. With regard to the last column, there is a "CAM assay procedure" described on page 16, but this appears to be unrelated to the Table 4. That procedure does not yield IC(50) results; it gives instead the data presented in the Figure 1, and was done on compounds of unspecified structure.

(6) Skill of those in the art: For the skill level in terms of RTKs, see section (4) above.

In terms of cancer: It is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. As an example, one skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. The majority of common cancers do not respond to chemotherapy.

The skill level in the area of angiogenesis is particularly low, relative to the difficulty of task. It is true that the use of such compounds to treat cancer has been researched for over 30 years, beginning with the pioneer research of Dr. Judah Folkman. The grand total of actual anticancer drugs which have come from this research, as of the filing date, is ZERO. The anti-angiogenisis area is indeed the most active area of cancer research ever to have existed which (as of early 2003) has not produced a single effective drug. The skill level is so low that even extremely positive initial animal results cannot be converted into actual use. As an example, there is cited Kolata, "Two Drugs Eradicate Tumors in Mice" New York Times 5/3/1998, http://www.shamema.com/cancer-c.htm downloaded from the Internet 3/28/03. Speaking of angiostatin and endostatin, the article says, "Some cancer researchers say the drugs are the most exciting treatment that they have ever seen." Dr. Richard Klausner, the (now former) National Cancer Institute Director called them "the single most exciting thing on the horizon" for the treatment of cancer. "Judah is going to cure cancer in two years," said Dr. James Watson, a Nobel laureate. However, as is seen by the reference, Marshall, "Setbacks for Endostatin" Science 295, 2198-2199 (February 2002) the skill level is so low that researchers cannot even replicate each other's results! The scientists reported "we detected neither inhibition of [blood vessel growth] nor antitumor activity." The article goes on to quote Robert Kerbel as saying that the pharmacokinetics of anti-angiogenesis may be "very complex", and describes how some scientists, once enthusiastic, have become skeptics. Even Dr. Folkman cannot resolve the paradoxical results, saying "The mechanism of this paradox is unknown."

There is nothing unique about this failure. Recent Phase III trial failures include SU5416 (semaxanib), on advanced colorectal cancer; BB-2516 (marimastat), on at least 6 different cancers; AG-3340 (prinomastat), on hormone refractory prostate cancer, and non-small cell; Bay-12-9566 (tanomastat), on Pancreatic cancer, and small cell lung cancer; IM-862, on Kaposi's Sarcoma. In fact, the trial with tanomastat on SCLC actually showed that the cancer progressed faster in the treated group than the non-treated group. Still others failed the phase II trials. The reference "Learning from Angiogenesis Trial Failures" http://www.genomics.org.cn:8080/bgi/english/news/englishnews%20020320-4.htm downloaded from the Internet 3/26/03 discusses these problems, looking a 12 recent phase III failures. Difficulties are noted in planning trials for these drugs, and substantial problems determining endpoints and even modes of administration. It is clear that, unlike other areas of anti-cancer research, preclinical testing and even phase II results of anti-angiogenesis agents are not a reliable indicator of success, since every Phase III trial has been a failure.

For a more comprehensive view of the difficulties of treating cancer with anti-angiogenisis agents, there is cited Sweeney et al, Trends in Molecular Medicine Volume 9(1), January 2003, Pages 24-29. Table 2 shows many forms that resistance takes to these agents, including endothelial and tumor cell heterogeneity, the presence of survival factors within the tumor micro-environment, the problem of defining the best dose and schedule for anti-angiogenic therapies, and angiogenesis-independent regrowth of tumors. The conclusion states, "advances in our knowledge of fundamental cancer biology are required before anti-angiogenic therapies can be integrated into

routine clinical practice." This is a clear statement that more than routine experimentation is needed.

(7) The quantity of experimentation needed: As a result of points 1), 3), 4), 5) and 6) above, the quantity of experimentation is expected to be quite extensive.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Applicants have cited the Chong patent, but each case is evaluated on its own merits; that patent did not issue on this specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

June 23, 2003